ACID-BASE HOMEOSTASIS OF THE NEWBORN INFANT DURING THE FIRST 24 HOURS OF LIFE

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THE low CO_2 content and Pco_2 of the blood of newborn infants, as compared with that of adults, have been frequently reported.[1-6] These findings have been the basis for (1) the concept of a persistent metabolic acidosis,[3, 4] (2) a theoretical explanation of the respiratory drive,[5] and (3) speculation concerning the utilization of anaerobic metabolism for energy in the newborn.[3, 4] However, the blood of women during the last trimester of pregnancy also shows diminished CO_2 content and Pco_2.[7-15] The cause of this change is not known; it has been attributed to hyperventilation,[13] and to the effect of progesterone.[14] Total plasma base is reduced by 8 mEq./L.,[10] but plasma organic acids are normal[11] or reduced.[10] It is the purpose of this paper to compare the acid-base balance of newborn infants with that of pregnant women and to discuss the possible significance of this relationship.

MATERIALS AND METHODS

Umbilical arterial bloods were collected from clamped segments of umbilical cord and were taken to represent the status of the infant's systemic arterial blood at the end of parturition. The analyses of these bloods have been presented.[16] Left atrial samples were drawn from newborn infants during the first hour after birth or at the third hour and again at approximately 24 hours, during atrial catheterization via the umbilical vein. It was not technically possible to sample all infants serially. All infants were quiet during the procedure, many of them sleeping. All weighed over 2,500 grams and were born vaginally or by cesarean section of nondiabetic, nontoxemic mothers. Only bloods of infants with an Apgar score[17] of 6 or better were reported. All infants received routine nursery care, which included a feeding of glucose water at about 8 hours of age, and formula or breast feeding between 12 and 24 hours.

Maternal arterial blood samples were drawn at the time of secondary cesarean section of mothers who were not in labor. Sections were performed under regional anesthesia. Demerol, 50 mg., and scopolamine, 0.4 mg., was the usual premedication, given an hour before surgery. No bloods are reported of any mother who was hyperventilating or restless, who had received inhalation anesthesia, or whose face had been covered with a mask prior to sampling.

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Bloods were collected anaerobically in greased syringes, the deadspaces of which were filled with a concentrated heparin solution. They were rotated through ice water until analyzed. Oxygen saturation, pH, carbon dioxide content, and hematocrit were determined by methods previously described.[16] The pH of atrial blood specimens was measured at 37° C. and was corrected to deep rectal (6-7 cm.) temperature, according to the formula of Rosenthal.[18] The P_{CO_2} was calculated from the Henderson-Hasselbalch equation, using pK′ and solubility coefficient of CO_2 corrected to the infant's body temperature according to the values of Severinghaus and his associates.[19, 20] The P_{CO_2} of the other bloods and the buffer base (BB) was determined from the Singer and Hastings nomogram.[21]

RESULTS

The results of the blood gas analyses are shown in Tables I-V. The mean values for 12 maternal samples (Table I) were pH—7.39; plasma CO_2 content—19.96 mEq./L.; P_{CO_2}—31.7 mm. Hg; and BB—41.8 mEq./L. of whole blood. Despite our maternal control subjects not having been in a basal state, our value for P_{CO_2} was in good agreement with the alveolar P_{CO_2} tension determinations of other authors, which are tabulated below.

Author	*P_{CO_2}, mm. Hg*
Rowe[8]	29.9 and 30.9
Goodland et al.[14]	30 (approximately)
H. and E. Bouterline-Young[15]	30.9
Present study	31.7

Our value for arterial plasma CO_2 content was somewhat lower than the venous plasma values of other authors, which are tabulated below.

Author	*Plasma CO_2, mEq./L.*
Dennis and King[9]	23.1 (venous)
Oard and Peters[10]	22.1 (venous)
Stander et al.[11]	21.8 (venous)
Muntwyler et al.[12]	22.7 (venous)
Present study	19.96 (arterial)

Our value for pH was within the normal adult range and confirms the findings of Kydd.[22]

The data of Tables II-VI indicate that the infant is subjected to a period of anoxia, CO_2 retention, and acidosis during parturition which recede rapidly after birth. At 24 hours of age

TABLE I. ACID-BASE BALANCE OF 12 PREGNANT WOMEN AT TERM
ARTERIAL SAMPLES

	OXYGEN SATURATION (PER CENT)	PH BLOOD	P_{CO_2} MM. HG	CO_2 CONTENT MEQ./L. PLASMA	BUFFER BASE MEQ./L. BLOOD
Dov	95.1	7.38	35	21.3	42.0
Rod	95.0	7.44	28	19.2	42.2
Jac	96.6	7.37	30	18.0	40.2
Ric	96.4	7.42	31	20.1	42.3
Fol	93.7	7.34	35	19.5	40.2
Han	93.4	7.39	32	19.5	40.8
Burn	95.1	7.31	33	17.3	37.4
Bea	96.5	7.47	33	24.4	47.2
Mag	93.6	7.39	33	20.3	41.3
Burk	97.6	7.42	26	17.4	43.0
Lev	95.0	7.41	30	19.9	42.0
Men	94.0	7.39	35	22.6	43.5
Average	95.17	7.393	31.7	19.96	41.84
S.D.	1.36	0.043	2.8	2.08	2.23

TABLE II. ACID-BASE BALANCE DURING BIRTH OF 21 INFANTS
UMBILICAL ARTERY SAMPLES

	TYPE OF DELIVERY	OXYGEN SATURATION (PER CENT)	pH BLOOD	P_{CO_2} MM. HG	CO_2 CONTENT MEQ./L. PLASMA	BUFFER BASE MEQ./L. BLOOD
Lob	Vaginal	0.0	7.32	44	20.5	41.5
Tor	Vaginal	9.2	7.28	46	22.3	39.6
Dov	Cesarean	0.0	7.23	64	26.5	41.4
Vel	Vaginal	7.0	7.12	64	21.6	33.7
Aie	Cesarean	8.2	7.22	64	27.0	41.7
Lor	Cesarean	23.9	7.27	53	25.5	42.1
Dod	Cesarean	30.9	7.30	50	25.7	43.0
Cha	Cesarean	47.8	7.26	49	23.8	40.9
Jac	Cesarean	30.1	7.28	—	—	—
Rod	Cesarean	30.9	7.30	43	22.5	44.8
Pie	Vaginal	17.2	7.20	63	26.2	40.5
Hal	Vaginal	30.5	7.15	64	23.7	37.1
Bea	Cesarean	4.0	7.20	67	28.3	41.3
Mag	Cesarean	21.1	7.22	54	23.3	39.3
Sch	Cesarean	7.0	7.10	64	21.4	33.7
Mel	Vaginal	9.4	7.23	53	23.2	38.4
Burk	Cesarean	28.1	7.27	50	24.3	41.2
Men	Cesarean	39.5	7.30	54	28.3	44.8
Mon	Vaginal	2.2	7.20	62	25.6	39.2
Rei	Vaginal	0.0	7.18	59	23.5	37.0
Gib	Vaginal	10.5	7.22	92	38.6	51.7
	Average	17.02	7.231	58.4	25.04	40.65
	S.D.	14.41	0.062	10.5	3.89	3.98

TABLE III. ACID-BASE BALANCE DURING FIRST HOUR OF 10 INFANTS
LEFT ATRIAL SAMPLES

	TYPE OF DELIVERY	OXYGEN SATURATION (PER CENT)	pH BLOOD	P_{CO_2} MM. HG	CO_2 CONTENT MEQ./L. PLASMA	BUFFER BASE MEQ./L. BLOOD
Woo	Vaginal	93.8	7.31	37	21.3	42.0
Jac	Cesarean	91.7	7.43	28	20.4	44.8
Ric	Cesarean	88.1	7.22	51	22.8	40.5
Burn	Vaginal	94.9	7.22	48	21.2	40.3
Tho	Vaginal	97.4	7.30	42	21.7	42.8
Hal	Vaginal	93.2	7.26	38	18.6	39.5
Bea	Cesarean	94.0	7.35	41	24.3	46.8
Mag	Cesarean	96.0	7.25	34	16.2	37.5
Mel	Vaginal	94.0	7.29	38	19.5	41.1
Del	Vaginal	95.2	7.41	31	20.2	46.4
	Average	93.83	7.304	38.8	20.62	42.17
	S.D.	2.55	0.023	7.3	2.27	3.39

TABLE IV. ACID-BASE BALANCE AT THIRD HOUR OF 7 INFANTS
LEFT ATRIAL SAMPLES

	TYPE OF DELIVERY	OXYGEN SATURATION (PER CENT)	pH BLOOD	P_{CO_2} MM. HG	CO_2 CONTENT MEQ./L. PLASMA	BUFFER BASE MEQ./L. BLOOD
Han	Cesarean	98.0	7.29	46	22.5	41.9
Pie	Vaginal	94.4	7.37	36	22.6	46.3
Wal	Cesarean	95.1	7.35	39	23.4	44.8
Burk	Cesarean	95.1	7.31	39	21.3	42.4
Duc	Vaginal	94.4	7.35	41	22.9	45.2
Per	Vaginal	93.2	7.37	32	19.2	43.8
Fly	Vaginal	92.6	7.35	35	21.2	43.2
	Average	94.69	7.341	38.3	21.87	43.94
	S.D.	1.73	0.030	6.1	1.42	1.58

TABLE V. ACID-BASE BALANCE AT 24 HOURS OF 14 INFANTS
LEFT ATRIAL SAMPLES

	TYPE OF DELIVERY	OXYGEN SATURATION (PER CENT)	pH BLOOD	P_{CO_2} MM. HG	CO_2 CONTENT MEQ./L. PLASMA	BUFFER BASE MEQ./L. BLOOD
Burn	Vaginal	92.2	7.35	37	21.1	42.8
Pie	Vaginal	91.7	7.36	39	23.5	45.3
Tho	Vaginal	93.1	7.37	35	21.4	43.8
Mag	Cesarean	98.0	7.39	35	21.7	43.2
Del	Vaginal	96.6	7.42	31	21.1	46.9
Lop	Vaginal	98.0	7.42	31	20.5	46.5
Sil	Vaginal	92.0	7.40	28	18.2	43.5
Bir	Vaginal	86.4	7.48	30	22.5	46.4
Cro	Vaginal	97.5	7.42	33	21.9	46.5
Reu	Cesarean	86.9	7.49	37	20.5	44.5
Sto	Cesarean	97.2	7.41	33	21.8	44.2
Gav	Cesarean	91.9	7.40	37	24.0	47.6
Fly	Vaginal	91.0	7.40	35	22.7	44.9
Bar	Vaginal	92.2	7.41	29	18.6	40.3
	Average	93.19	7.408	33.6	21.38	44.74
	S.D.	3.85	0.039	3.4	1.63	1.98

TABLE VI. STATISTICAL COMPARISON OF INFANT BLOOD VALUES AT EACH TIME WITH MATERNAL CONTROLS*

	pH	p	P_{CO_2}	p	CO_2 CONTENT	p	BUFFER BASE	p
Birth (Umb. A.)	7.23	<.01	58.4	<.01	25.04	<.01	40.7	>.10
During first hour	7.30	<.01	38.8	<.02	20.62	>.10	42.2	>.50
At third hour	7.34	<.01	38.3	<.01	21.87	<.05	43.9	<.05
At 24 hours	7.41	>.10	33.6	>.10	21.38	>.05	44.7	<.01
Maternal	7.39		31.7		19.96		41.8	

*p values less than 0.05 are taken to represent statistically significant differences between maternal and infant values.

there is no statistical difference between the means of maternal and infant pH, P_{CO_2}, and CO_2 content. The newborn child would seem to move toward the level of pH and P_{CO_2} to which he was exposed in utero.

Fig. 1 is a plot of the pH and CO_2 content data taken from Tables I-V, showing the changes which occur through time with respect to our maternal control values and to normal adult values as given by Peters and Van Slyke.[23]

In Fig. 2 the results obtained by Graham and Wilson[5] from heel capillary blood of 24-hour-old infants is presented. In this method, blood is obtained by pricking the heel and collecting the blood under mineral oil. The ensuing crying of the infant and the possible loss of CO_2 into the mineral oil may cause variation from basal arterial values. The results of Marples and Lippard[2] for *venous* blood of 1- to 8-day-old infants are shown in Fig. 3. (Comparable *arterial* blood of these infants could be expected to contain 1.5 to 2 mEq./L. less CO_2, bringing these data even closer to the range of maternal control values.) The results of these laboratories tend to confirm our finding that although newborn infants have a CO_2 deficit with respect to normal adults, no such deficit exists with respect to pregnant women near term.

Buffer base rises steadily from birth to a mean level of 44.7 mEq./L. of whole blood at age 24 hours, a value

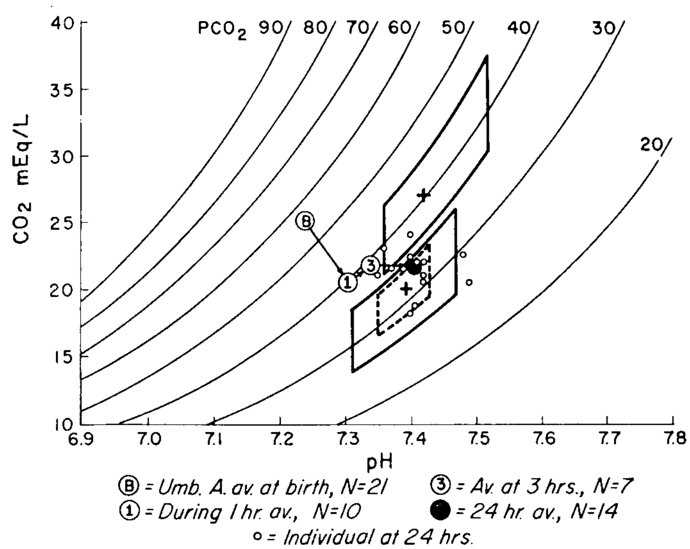

Fig. 1.—The ordinate is mEq./L. plasma CO_2. The abscissa is pH. The curved lines are P_{CO_2} isobars and are logarithmically spaced. The upper quadrilateral represents the range of normal adult arterial values. The lower quadrilateral represents the range of maternal arterial values, with one S.D. from the mean indicated by broken lines.

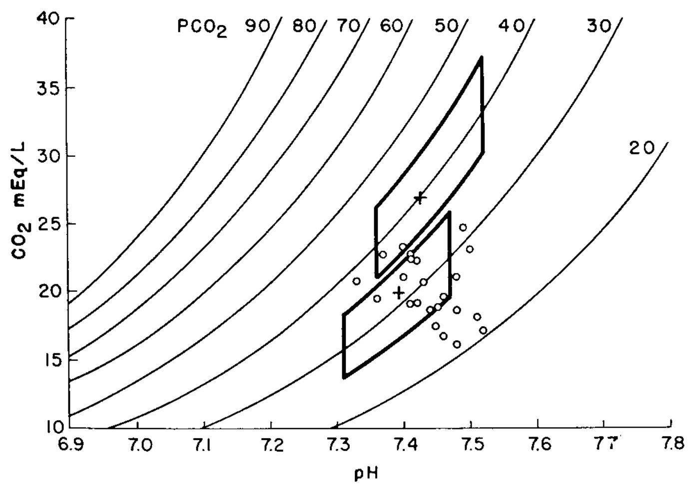

Fig. 2.—Capillary (arterial) blood—24 hours of age. Data of Graham and Wilson[5] plotted as open circles. The quadrilaterals represent normal arterial values and data from pregnant women, respectively, as in Fig. 1.

which is higher than the maternal level but lower than the mean normal adult value of 49 mEq./L.[21] tion and accumulation of intermediary organic acids leading to a metabolic acidosis.

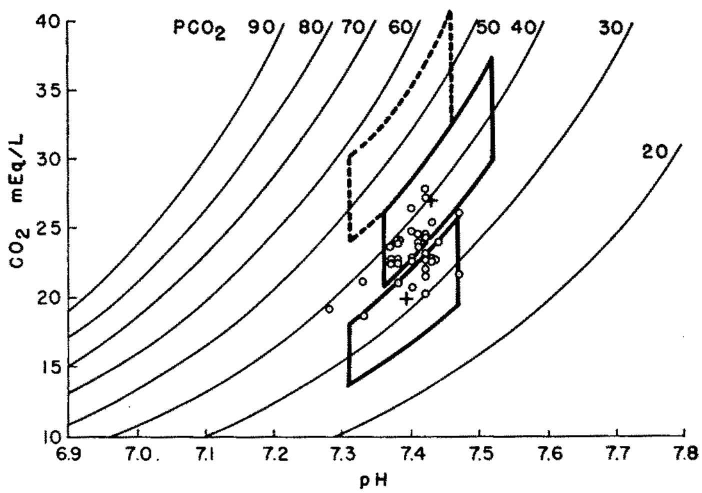

Fig. 3.—Venous blood—ages 1-8 days. Data of Marples and Lippard[2] plotted as open circles. Upper quadrilateral, outlined by dashed lines, includes additional range of adult normal venous blood. Lower quadrilaterals are as for Figs. 1 and 2.

DISCUSSION

From the data of Tables I-VI and Fig. 1, it appears that after the stress of parturition the homeostatic mechanisms of the newborn are directed toward attaining a pH and P_{CO_2} which existed in utero. In reviewing the early work attempting to establish the relation between maternal and fetal CO_2 tension, Barcroft[24] concludes that only a small difference should be expected. Barron,[25] in careful experiments on sheep, has shown that the alkali reserve of the ewe and that of its near-term fetus are almost identical.

Previous attempts to explain the low P_{CO_2} and CO_2 content of the blood of newborn infants dealt chiefly with two hypotheses, as follows: (1) the possibility that hyperventilation due to anoxia caused lowering of P_{CO_2} and (2) the possibility that anaerobic metabolism caused lessened CO_2 produc-

Hyperventilation Due to Anoxia Hypothesis.—Graham and Wilson have explained the low P_{CO_2} of babies at 24 hours of age as the result of hyperventilation due to anoxic stimulation of the aortic and carotid chemoreceptors. During the first hour of life, they noted oxygen saturation of capillary blood from the heel to the level of 85 per cent, corresponding to an O_2 tension of 50 mm. Hg. They do not state whether the heel was arterialized by warming prior to sampling. Persistent cyanosis of the feet is common in healthy infants during the first day and probably represents local circulatory stasis rather than systemic arterial desaturation. Left atrial saturations during the first day are given in Tables III-V. The saturation is about 94 per cent during the first hour and does not change appreciably with time. These results confirm our suspicion that heel capillary blood may not represent true arterial samples.

We may assume that the respiratory center of the fetus in utero adapts to the low P_{CO_2} environment supplied by its mother and that the rise in P_{CO_2} during parturition supplies one of the chemical drives to respiration, subsequently. It is known in animals that experimental elevation of maternal P_{CO_2} will cause respiratory movements of the fetus in utero.[26]

The exact nature of the hypoxic chemoreceptor drive to respiration in newborn infants is not clear. Cross and Warner[27] have demonstrated a small rise in minute volume during the first week of life in infants exposed to an atmosphere of 15 per cent O_2, while Miller and Behrle[28] have not recorded such a rise in infants, one day old or less, given 12 per cent O_2 (approximate alveolar P_{O_2} of 50 mm. Hg). Thus, the level of arterial P_{O_2} at which Graham and Wilson postulate a strong hypoxic stimulus may not actually produce one. Moreover, the recent work of James and Rowe[29] indicates that very low oxygen tensions cause profound circulatory changes which further decrease systemic arterial saturation. However, both Cross[30] and Miller[31] agree that CO_2 is a potent stimulus to respiration. We postulate that the low P_{CO_2} of the newborn at 24 hours represents the end results of the respiratory center's efforts to attain a level of P_{CO_2} similar to that to which it had been exposed in utero.

Anaerobic Metabolism With Production of Organic Acids and Metabolic Acidosis Hypothesis.—Wilson and his associates[3] postulated that anaerobic metabolism, with diminished CO_2 production, accounted for the low plasma CO_2 content of newborn infants. They cited the prolonged survival time of newborn laboratory animals made severely anoxic as additional proof of the role of anaerobic metabolism in young animals. However, the ability of young laboratory animals to survive anoxic stress is not necessarily proof of increased capacity for anaerobic metabolism over that of the adult. Villee and Kimmelstiel[32] have calculated that anaerobic glycolysis will probably not provide sufficient energy to explain survival in these animals. Moreover, in clinical obstetrics, the infant can withstand only a few minutes of anoxia such as might occur during impaction of the shoulders.

Graham and co-workers[4] have shown the plasma "R" fraction (which consists largely of organic acids) to be 15 mEq./L. for 24-hour-old infants, whereas that of the adult is only 10 mEq./L. Räihä,[33] in discussing fetal tissue metabolism, states, "The acidosis demonstrated in the newborn is largely due to organic acids, chiefly to pyruvic and lactic acids. . . ." The blood pyruvate level he observed was 1.18 mg. per cent or 0.52 mg. per cent above adult levels. Gonzales and Gardner[34] have shown a similar difference in pyruvate level between infants during the first 24 hours of life and pregnant women. Such a difference would contribute about 0.1 mEq./L. of plasma to the excess "R" value. Blood lactate levels in somewhat older infants were found by Brehme[35] to be 8 mg. per cent above adult levels, which would contribute only about 1.2 mEq./L. of plasma to the "R" value. Thus, the products of anaerobic glycolysis account for only one quarter of the excess "R" value. Leopold and Bernhard[36] found no relation between lactate level and CO_2 combining power in older children.

The data of Tables II-V indicate that buffer base rises steadily after birth, but that at 24 hours it is still below the normal adult level of 49 mEq./L. (though higher than the maternal level). Reduction of buffer base means, by definition, metabolic acidosis. However, it is not necessary to assume that this acidosis is a result of increased capacity of the fetus and newborn for anaerobic glycolysis. Holaday and associates[37] have demonstrated in anesthetized man and animals that CO_2 retention is capable of producing a prolonged fall in buffer base by a mechanism yet to be elucidated. The work of Singer and his colleagues, quoted by Dripps and Severinghaus,[38] indicates the possibility of migration of hydrogen ion from the cell to the extracellular fluid during CO_2 retention. It is possible that CO_2 retention during parturition induces a similar change in the human infant. Further investigation of the acid-base balance of the fetus in utero is necessary to answer this question.

SUMMARY AND CONCLUSIONS

In evaluating the significance of the low P_{CO_2} and CO_2 content in the blood and plasma of newborn infants, consideration should be given to the fact that this state also exists in the pregnant woman during the last trimester. Interpretations of the status of the newborn infant's respiratory drives and acid-base metabolism made with respect to normal adult values may be misleading.

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REFERENCES

1. Hoag, L. A., and Kiser, W. H., Jr.: Acid-Base Equilibrium of Newborn Infants, Am. J. Dis. Child. **41**: 1054, 1931.
2. Marples, E., and Lippard, V. W.: Acid-Base Balance of Newborn Infants, Am. J. Dis. Child. **44**: 31, 1932.
3. Wilson, J. L., Reardon, H. S., and Murayama, M.: Anaerobic Metabolism in the Newborn Infant, Pediatrics **1**: 581, 1948.
4. Graham, B. D., Wilson, J. L., Tsao, M. U., Bauman, M. L., and Brown, S.: Development of Neonatal Electrolyte Homeostasis, Pediatrics **8**: 68, 1951.
5. Graham, B. D., and Wilson, J. L.: Chemical Control of Respiration in Newborn Infants, A. M. A. Am. J. Dis. Child. **87**: 287, 1954.
6. Gottfried, S. P., Bogin, M., and Levycky, N. V., Jr.: Blood and Electrolyte Studies on Normal Newborn Full-Term Babies, A. M. A. Am. J. Dis. Child. **87**: 543, 1954.
7. Marrack, J., and Boone, W. B.: The Acid-Base Balance in the Plasma in the Later Stages of Pregnancy, Brit. J. Exper. Path. **4**: 261, 1923.
8. Rowe, A. W.: Studies in the Metabolism of Pregnancy, J. Biol. Chem. **55**: Sci. Proc. xxviii, 1923.
9. Dennis, W., and King, E. L.: A Chemical Study of the Inorganic Constituents of Blood in Normal and Abnormal Pregnancy, Am. J. Obst. & Gynec. **7**: 253, 1924.
10. Oard, H. C., and Peters, J. P.: The Concentration of Acid and Base in the Serum in Normal Pregnancy, J. Biol. Chem. **81**: 9, 1929.
11. Stander, H. J., Eastman, N. J., Harrison, E. P. H., Jr., and Cadden, J. F.: The Acid-Base Equilibrium of the Blood in Eclampsia, J. Biol. Chem. **85**: 233, 1929.
12. Muntwyler, E., Lumback, N., Bill, A. H., and Meyers, V. C.: The Acid-Base Equilibrium of the Blood in Pathological Conditions, J. Biol. Chem. **90**: 607, 1931.
13. Plass, E. D., and Oberst, F. W.: Respiration and Pulmonary Ventilation in Normal Non-Pregnant, Pregnant and Puerperal Women, Am. J. Obst. & Gynec. **35**: 441, 1938.
14. Goodland, R. L., Reynolds, J. G., and Pommerenke, W. J.: Alveolar CO_2 Tension Levels During Pregnancy and Early Puerperium, J. Clin. Endocrinol. **14**: 522, 1954.
15. Bouterline-Young, H., and Bouterline-Young, E.: Alveolar Carbon Dioxide Levels in Pregnant, Parturient and Lactating Subjects, J. Obst. & Gynaec. Brit. Emp. **63**: 509, 1956.

16. James, L. S., Weisbrot, I. M., Prince, C. E., Holaday, D. A., and Apgar, V.: The Acid-Base Status of Human Infants in Relation to Birth Asphyxia and the Onset of Respiration, J. PEDIAT.

17. Apgar, V.: A Proposal for a New Method of Evaluation of the Newborn Infant, Anesth. & Analg. 32: 260, 1953.

18. Rosenthal, T. B.: The Effect of Temperature on the pH of Blood and Plasma in Vitro, J. Biol. Chem. 173: 25, 1948.

19. Severinghaus, J. W., Stumpfel, M., and Bradley, A. F.: Variations of Serum Carbonic Acid pK' with pH and Temperature, J. Appl. Physiol. 9: 197, 1956.

20. Severinghaus, J. W., Stumpfel, M., and Bradley, A. F.: Accuracy of Blood pH and pCO_2 Determinations, J. Appl. Physiol. 9: 189, 1956.

21. Singer, R. B., and Hastings, A. B.: An Improved Clinical Method for Estimation of Disturbance of the Acid-Base Balance of Human Blood, Medicine 27: 223, 1948.

22. Kydd, D.: Hydrogen Ion Concentration and Acid-Base Equilibrium in Normal Pregnancy, J. Biol. Chem. 91: 63, 1931.

23. Peters, J. P., and Van Slyke, D. D.: Quantitative Clinical Chemistry, Baltimore, 1931, Williams & Wilkins Co., vol. I, pp. 940-941.

24. Barcroft, J.: Researches on Pre-natal Life, Springfield, 1947, Charles C Thomas, Publisher, pp. 179-180.

25. Barron, D. H.: A Comparative Study of the Alkali Reserve of Normal, Pregnant and Fetal Sheep, Yale J. Biol. Med. 26: 119, 1953.

26. Whitehead, W. H., Windle, W. F., and Becker, R. F.: Changes in Lung Structure During Aspiration of Amniotic Fluid and During Air-Breathing at Birth, Anat. Rec. 83: 255, 1942.

27. Cross, K. W., and Warner, P.: The Effect of Inhalation of High and Low Oxygen Concentrations on the Respiration of the Newborn Infant, J. Physiol. 114: 283, 1951.

28. Miller, H. C., and Behrle, F. C.: The Effects of Hypoxia on the Respiration of Newborn Infants, Pediatrics 14: 93, 1954.

29. James, L. S., and Rowe, R. D.: The Pattern of Response of Pulmonary and Systemic Arterial Pressures in Newborn and Older Infants to Short Periods of Hypoxia, J. PEDIAT. 51: 5, 1957.

30. Cross, K. W., and Hooper, J. M. D.: The Effect of CO_2 on the Respiration of the Full-Term and Premature Infant, J. Physiol. 119: Proc. Physiol. Soc., p. 2, 1952.

31. Miller, H. C.: The Effect of High Concentrations of Carbon Dioxide and Oxygen on the Respiration of Fullterm Infants, Pediatrics 14: 104, 1954.

32. Villee, C. A. and Kimmelstiel, R.: Effects of Anoxia on Intermediary Metabolism in Fetal Tissues, Études Néonatales 4: 3, 1955.

33. Räihä, C. E.: Tissue Metabolism in the Human Fetus, in Cold Spring Harbor Symposia on Quantitative Biology, Vol. XIX, Long Island Biological Association, 1954, p. 146.

34. Gonzales, R. F., and Gardner, L. I.: Concentration of Pyruvic Acid in the Blood of the Newborn Infant, Pediatrics 19: 844, 1957.

35. Brehme, T.: Über den Milchsäuregehalt des Blutes im Säuglingsalter, Monatschr. Kinderh. 34: 456, 1929.

36. Leopold, J. S., and Bernhard, A.: Lactic Acid in the Blood in Children, Am. J. Dis. Child. 41: 758, 1931.

37. Holaday, D. A., Ma, D., and Papper, E. M.: The Immediate Effects of Respiratory Depression on Acid-Base Balance in Anesthetized Man, J. Clin. Invest. 36: 1121, 1957.

38. Dripps, R. D., and Severinghaus, J. W.: General Anesthesia and Respiration, Physiol. Rev. 35: 741, 1955.